

EDITORIAL REVIEW

The skin immune system and psoriasis

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Our concept of the skin as the most peripheral outpost of the immune system has evolved considerably over the past decade. So far from purely subserving a barrier function, the skin contains all the elements of an intrinsic immune system, comprising lymphocytes and antigen-presenting $CD1^+DR^+$ Langerhans' cells, which circulate between the epidermis and the regional lymph nodes, dermal antigen-presenting cells (including perivascular factor XIIIa⁺ dermal dendritic cells), and keratinocytes which produce a wide range of immunoregulatory cytokines [1–4]. Epidermal keratinocytes have been shown to secrete (particularly when damaged) [3] IL-1, IL-6, IL-7, IL-8 and IL-10, tumour necrosis factor- α (TNF- α), the colony stimulating factors (CSF) IL-3, granulocyte/macrophage-CSF, granulocyte-CSF, and macrophage-CSF, growth factors including transforming growth factor (TGF) α and β , platelet-derived growth factor, and basic fibroblast growth factor, as well as α -melanocyte stimulating hormone (α -MSH) and a specific inhibitor of IL-1 termed IL-1 receptor antagonist (IL-1Ra) [5,6]. In general, IL-1, IL-6, IL-7, IL-8 and TNF- α have pro-inflammatory properties, while IL-10, TGF- β , α -MSH and IL-1Ra down-regulate cutaneous inflammation.

The importance of the superficial skin vasculature to the functioning of the skin immune system has only recently been appreciated. Interactions between sets of adhesion molecules on leucocytes, and on dermal endothelial cells such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and endothelial-leucocyte adhesion molecule-1 (E-selectin), are critical to the recruitment of inflammatory cells into the skin [7,8]. E-selectin may act as a vascular addressin for memory T cell homing to the skin, since the ligand for E-selectin on T cells is highly restricted to a specific subset of memory T cells, and E-selectin (in contrast to ICAM-1 and VCAM-1) reportedly shows biased expression on inflamed endothelium of skin [9]. Expression of these endothelial cell adhesion molecules is up-regulated by IL-1 and TNF- α [10,11]. It has therefore been proposed that injured keratinocytes are able to initiate cutaneous inflammation directly, in an antigen-independent fashion, by IL-1- and TNF- α -induced inflammatory cell recruitment [8]; antigen-dependent mechanisms of amplification and persistence of inflammation, involving T cell–Langerhans' cell or –dermal macrophage interactions, would

then supervene. Keratinocyte expression of ICAM-1, induced by interferon- γ (IFN- γ) produced by infiltrating T cells, may be important in determining the exocytosis of leucocytes into the epidermis, seen in many inflammatory dermatoses [12].

Psoriasis, a genetically determined inflammatory and proliferative skin disorder with a population prevalence of between 1.5% and 3% [13], is now thought to involve, at least in part, dysregulation of the skin immune system [5,6,14–18]. This hypothesis is supported by the clinical efficacy of treatment with cyclosporin A [19], since this drug has inhibitory effects on epidermal antigen-presenting cell function, T cell activation and lymphokine release, and leads to clearing of immunocompetent cells from the skin before clinical effects are evident. Abnormalities in all of the elements of the skin immune system have been documented in psoriasis. In this issue of *Clinical and Experimental Immunology*, Lee *et al.* [20] review the literature on lymphocyte attachment to endothelium in psoriasis. Cytokines including IL-1, TNF- α , IFN- γ and IL-4, which stimulate endothelial cell adhesiveness for lymphocytes, may be up-regulated in psoriasis [8,21,22]; superficial dermal post-capillary venules in psoriatic skin are strongly ICAM-1⁺, and endothelial cells also express ELAM-1 and VCAM-1 [8]. Baseline, and IL-1- and TNF- α -induced increases in, lymphocyte adherence to cultured normal dermal microvascular endothelial cells is inhibited by TGF- β ; by contrast, psoriatic dermal microvascular endothelial cells show specific unresponsiveness to the effects of TGF- β [22]. Lee *et al.* [20] report that lymphocytes from psoriasis patients, when compared with those from controls and patients with atopic dermatitis or rheumatoid arthritis, demonstrate specific augmented binding to cultured human umbilical vein endothelial cells, by a cytokine-independent mechanism. This is of considerable interest, since it suggests that the prominent cutaneous inflammation characteristic of psoriatic skin lesions may involve abnormalities in both lymphocytes and endothelial cells.

It has been proposed that persistent T cell stimulation may occur in psoriasis as a result either of presentation of foreign (e.g. microbial) antigen by antigen-presenting cells, or as a result of autoreactivity [14,15,18]. The dermal infiltrate in psoriatic lesional skin contains mainly T lymphocytes, chiefly of $CD4^+$ type with an admixture of $CD8^+$ cells, and macrophages [14,18]. $CD4^+/CDw29^+$ helper-inducer T cells predominate over $CD8^+/CD45R^+$ suppressor-inducer T cells in sections of, and cell lines established from, both lesional and uninvolved psoriasis skin [23]. T cells proliferating in the dermis of patients with psoriasis are primarily recall antigen-reactive helper T cells

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[24]. There is an overall increase in the number and function of antigen-presenting cells capable of activating autologous T cells in lesional skin; these include epidermal and dermal Langerhans cells, as well as CD1-DR⁺ non-Langerhans antigen-presenting cells, such as lymph node-based RFD-1⁺ interdigitating reticulum cells and factor XIIIa⁺ perivascular dendritic cells [4,18,25]. Epidermal antigen-presenting cells from psoriatic lesional skin resemble lymphoid dendritic cells rather than freshly isolated normal Langerhans' cells, in their response to treatment with TGF- β or chloroquine, and their capacity to induce vigorous stimulation of autologous T cells [26,27]. This has resulted in a proposal that psoriasis involves inappropriate T cell activation in the epidermis due to abnormal Langerhans cell function [17,26,27]. In this regard, it is of interest that 20% of epidermal T cells in psoriatic lesions express activation markers, compared with only 5% of dermal T cells, implying that entry into the epidermis is associated with activation [16]. Supernatants from cloned T cells propagated from psoriatic lesions contain lymphokines capable of inducing ICAM-1 and HLA-DR expression on cultured keratinocytes [18,28]. Activated T cells, and keratinocytes expressing ICAM-1, occur primarily in the suprapapillary regions of psoriatic lesions nearest the dermal capillaries.

Set against the evidence for T cell activation by antigen-presenting cells, is the fact that cell lines from psoriatic lesional skin have been reported to demonstrate autoreactivity, with possible specificity directed against minor HLA antigens [23]. T cell clones propagated from lesional skin in another study also demonstrated autoreactivity, in that they were activated by autologous epidermal cells from involved skin, and by autologous peripheral blood mononuclear cells [18]. Psoriatic lesional skin contains a population of OKM5⁺OKM1⁻ macrophage-like cells capable of triggering immunoregulatory T cell stimulation in the absence of antigen [18]. In addition, there may be ligands in psoriatic skin capable of direct activation of T cells via antigen-independent activating surface molecules such as CD2, CD28, or UM4D4 (CDw60); 75% of T cells in lesional skin, but only 20% of psoriatic peripheral blood cells, bind anti-UM4D4 MoAb [18,28].

Cytokines released from activated keratinocytes, or activated leucocytes, are now thought to play a major role in the immunopathogenesis of psoriasis. It has been proposed that keratinocytes, which lie in close proximity to the endothelial cells of the upper dermal vasculature in the region of the tips of the dermal papillae, may orchestrate inflammatory events in the dermis in psoriasis by secretion of pro-inflammatory cytokines with effects on the vasculature, such as IL-1 or TNF- α [7,8,10], or with chemotactic properties such as IL-8 [29,30]. IL-1 in particular has been the subject of interest, in view of its pro-inflammatory action *in vivo*, and its capacity to potentiate T cell activation, stimulate eicosanoid metabolism, induce fibroblast proliferation, up-regulate endothelial cell adhesion molecule expression, and potentially stimulate keratinocyte proliferation, all of which are features of psoriatic skin [5,6]. However, IL-1 bioactivity in lesional psoriatic skin has been reported to be markedly reduced relative to normal skin and to uninvolved psoriatic skin, although levels of non-functional IL-1 β are increased [31]. We and others have found the levels of IL-1Ra to be decreased in lesional psoriatic skin [5,6], but the ratio of IL-1Ra to IL-1 α , which is central to the net pro-inflammatory effect of IL-1, is reportedly greatly increased in stable psoriatic

plaques [5]. TGF- α , a potent autocrine growth factor for keratinocytes, is over-expressed in psoriatic epidermis [32]. IL-6, which is another growth factor for keratinocytes, is expressed at high levels in skin, monocytes and serum of patients with psoriasis, but not with atopic dermatitis [33,34]. IL-6 production by human dermal microvascular endothelial cells is up-regulated by IL-1 β and TNF- α [35]. Thus, cytokines known to be released within inflamed skin could contribute to the epidermal hyperproliferation seen in psoriasis.

The study of psoriasis has proved a useful biological model and testing ground for evaluation of the skin immune system. Unfortunately, the great majority of the abnormalities detected have not been unique to psoriasis, and we are still some way from understanding its cause and pathogenesis. Demonstration of a mechanism for lymphocyte recruitment to the skin apparently specific for psoriasis [20] is an important contribution to our knowledge of this distressing condition.

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